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Inappropriate benzodiazepine medical and non-medical use: a neglected problem begging for prevention

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Running head: Epidemiology of BDZ inappropriate use

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List of abbreviations:

BDZ, benzodiazepine

ED, emergency

EMCDDA, European Monitoring Center for Drugs and Drug Addiction

FDA, Food and Drugs Administration

GBD, Global Burden of Disease

GxE, gene and environment

HCW, healthcare workers

CI, confidence interval

OECD, Organisation for Economic Co-operation and Development (

OR, odds ratio

RR, relative risk

SUD, substance use disorder

VHA, Veteran Health Administration

Highlights:

- Medical and non-medical use of benzodiazepine is not systematically recorded.
- Almost half of the emergency department visits due to medication harm imply benzodiazepine use. Differential diagnosis plays a key role when addressing these adverse events.
- Social stigma contributes to hiding the phenomenon of benzodiazepine inappropriate use and related adverse events.
- Benzodiazepine users are often vulnerable to different comorbidities and have higher mortality risk for all causes than non-users.
- Deaths from overdose in which benzodiazepine are involved are increasing. Ascertainment of cause of deaths often does not include benzodiazepine inappropriate use, and does not distinguish between accidental or intentional overdose.

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Abstract

Aims: We aimed at providing an epidemiological overview on inappropriate use of benzodiazepines (BDZ) and its adverse outcomes. **Methods:** We performed a narrative review of recent studies focused on the epidemiology of BDZ inappropriate use. We addressed prevalence of use, incidence and possible predictors of life-threatening events, mortality risk, barriers to monitoring their use and to good prescription practice, screening and prevention of inappropriate use of BDZ. **Results:** Besides being good symptomatic medications, BDZ convey the risk of dependence and addiction, making their long-term use discouraged by the Food and Drugs Administration. BDZ prescription and long-term use are not systematically recorded, and therefore risky behaviors are scarcely documented. This prevents from attributing adverse events to BDZ use. While life-threatening events are well known in polysubstance intoxication, the specific effects of BZD non-medical use remain unrecognized. Ascertainment of cause of deaths often does not include BDZ, and does not distinguish between accidental or intentional overdose. Monitoring of BDZ use, preparedness of emergency departments, screening of at-risk subjects, sensitization of the general public and support for discontinuation treatments might help controlling BDZ inappropriate use. Further data are needed to characterize life-threatening events and deaths, and in turns help preventing a quote of the severe outcomes related to this medical problem. **Conclusions**: The inappropriate use of BDZ requires public health attention. Effective monitoring systems are needed to record and characterize BDZ use, especially when chronic. Health education programs targeting patients and providers should be promoted to recognize and control inappropriate use of BDZ.

Introduction

Benzodiazepines (BDZ) are widely used drugs, mainly prescribed for anxiety and sleep disorders (1). BDZ are generally considered safe, despite their potential adverse effects, especially in the chronic users (2,3). Based on this, the recommended duration of BDZ use is between 2 and 4 weeks (4). The correct medical practice also recommends avoiding these medications in individuals older than 65 or with history of substance use disorder (SUD) (5). The heterogeneity within the group of BDZ, mainly distinguished as short-acting and long-acting, should guide the choice of the best medication for the individual patient (5).

BDZ represents one of the main group of drugs of abuse. Blanco et al. estimated that 12.5% of US adults used BDZ in 2015-2016, and that, among the users, about 17% misused the drugs, and 1.5% had BDZ use disorders (6). Not only BDZ are linked to long-term problems including diversion, misuse and addiction, but they are also involved in at least one third of fatal overdoses, with an increasing trend in the last three decades (7). Specifically, BDZ are associated to increased all-cause mortality, with users dying at a 1.2- to 3.7-fold higher rate per year compared with non-users (7). However, disentangling the role played by underlying conditions, including baseline mental disorders, socioeconomic factors and lifestyle habits, from that of BDZ in causing death, remains challenging (7). Moreover, it is often difficult to weight the role of BDZ when multiple substance overdoses occur. Further, the accidental or intentional nature of an adverse outcomes from BDZ use is difficult to assess (8).

The aim of this paper was to provide evidence of the potential hazard of inappropriate BDZ use and to raise awareness around this problem, which requires specific attention on the identification of high-risk subjects and calls for higher adherence to the good prescribing guidelines.

EPIDEMIOLOGY OF BENZODIAZEPINE USE

The current Global Burden of Disease (GBD) database (2019) provides information on alcohol, opioid, cocaine, amphetamine, cannabis, and “other drug” use disorders, but does not include specific estimates regarding BDZ (9). According to the list of codes mapped to the GBD cause list, “other drug” use refers to use of hypnotics, tobacco, volatile solvents, multiple drug use[1] (9). Therefore, no accurate estimate of the burden of disease due to BDZ in particular is available today. Population-level data on BDZ use are fragmentary. As a result, it is difficult to capture the trend in BDZ use in the different countries (Table 1, [10-13]).

According to a recent cross-sectional study conducted among subjects older than 65, the prevalence of BDZ use varies significantly among countries, ranging from 14.5% in Germany to 44.1% in Israel, with zopiclone and lorazepam representing the most prescribed ones (12). This might reflect different prescription habits, regulations, and medical culture (12). BDZ prescription and mortality has considerably increased in the US, with people aged 50-64 reporting the highest use, and concerning rates of misuse being observed among aged 18-25 (13).

The last estimates produced by the Organization for Economic Co-operation and Development (OECD 2021) showed Italy and Turkey as the countries with the lowest chronic BDZ use (0.1 and 0.3 per 1000 subjects aged 65 and older, respectively) and long-acting BDZ use (0.3 and 1.2 per 1000 subjects aged 65 and older, respectively), with Iceland being at the top for chronic BDZ use (103.4 per 1000) and Estonia and Korea for long-acting BDZ use (129.4 per 1000 and 124.4 per 1000) (14). Notably, the largest decline in chronic BDZ use between 2009 and 2019 was observed in Iceland, and Korea experienced the largest decline in long-acting BDZ use. Country-specific factors may explain these variations (12).

SIDE EFFECTS OF BENZODIAZEPINE USE AND RISK FACTORS OF INAPPROPRIATE USE

Side effects related to use of benzodiazepines

BDZ adverse effects have been widely reported. Long-term neurocognitive impairment has been one of the most investigated adverse effects and was described in association to chronic BDZ use both in current and former users (15). This includes decline in different cognitive domains such as memory, language, attention, and processing speed (15). Also, individuals using BDZ are at higher risk of falls and vehicle accidents (16). Adverse pregnancy and delivery outcomes have also been reported in women exposed to BDZ (17). Other examples can be found in Table 2 (15-24). The symptoms following BDZ intoxication mainly involve the central nervous system, but respiratory depression may occur in case of particularly elevated intakes (19-22). This represents the most important symptom in a BDZ overdose, possibly leading to death. Withdrawal syndrome occurs in a subject who suspends too quickly the intake of the substance after its chronic use (21,22). It realizes different patterns, based on the doses assumed. Severity depends on factors associated to the drug (eg., potency, short- or long-action), the use (eg., dose and duration) and the subjects (eg., baseline anxiety) (21).

Notably, BDZ-related major events are connoted by psychological and physical symptoms which are often present in other major health emergencies, including electrolyte imbalance, acute hypoglycemia, stroke, or abuse of other substances (19). Because the use of psychotropic medications is subjected by social stigma, and given the compromising clinical presentation of major events related to their use, history of BDZ use remains often hidden (25,26). This complicates the identification and the management of subjects at risk of major events.

The role of genetics and environment in risky behaviors

Studies on genes and environment (GxE) had tried to distinguish for which extent the two components are implied under predisposition to SUD (27-32). GxE interaction refers to differences in genetic effects across levels of environmental exposure (28). The relationship between childhood stress and alcohol dependence in adult life is well known (29-34). Adverse events in childhood are also associated with early alcohol use, which in turn is related to higher risk of SUD later in life (34). Epigenetic mechanisms, including methylation and miRNAs, could mediate the role of the environment on patterns of differential gene expression in neurobiological systems of interest that can precipitate a SUD (34-37). Studies mainly addressed GxE interactions under SUD without focusing on a specific substance, or mainly focusing on alcohol, so it is unsure whether available evidence can also apply to BDZ (27,36). Furthermore, despite genetic associations have been reported in several studies, few have been replicated (27).

Other risk factors of benzodiazepine inappropriate use

Risk factors of inappropriate BDZ use have been identified. In Canada, the rates of non-medical BDZ use resulted low in general population, but higher in marginalized groups (e.g., unhoused people that use drugs) (2). Also, high and inappropriate prescribing were common in older adults. BDZ resulted associated with various morbidity outcomes (e.g., accidents/injuries, cognitive decline, sleep disturbances, or psychiatric issues), and were identified as a contributing factor in suicides and poisoning deaths (2).

According to recent estimates, 45% of the emergency department (ED) visits for medication harms involving abuse, misuse, or overdose without indication of intent involved BDZ (38). These resulted to be consumed with alcohol, marijuana, or illicit substances (eg., heroin, cocaine, unspecified opioids) in 66% of the ED visits for medication harms from nontherapeutic use (38).

Rooney et al. mapped the risk of BDZ overdose based on the electronic health records of patients admitted to ED for overdose in a hospital in Wisconsin (39). Of 419 cases, 40% were unintentional, and these were more likely to be reported by older, male, nonwhite, and who had no insurance (39). Bushnell and coworkers estimated that about 38,000 BDZ-related ED visits occurred in the US in 2016 among adolescent and young adults, with 40% of the women and 23% of the men being diagnosed with depression (40). Overall, 44% of these BDZ-poisonings were recorded as intentional (about 50% of the cases in women and 33% in men), and in both sexes multiple medications use was intentionally associated with BDZ, suggesting the importance of the risk assessment for suicide attempt in subjects with history of BDZ intoxication (40). A recent Italian study showed a higher proportion of ED visits related to use of BDZ than of opioids in young population, especially in women (41). The most common comorbidities recorded were mental health conditions, in particular 4% of the cases were diagnosed with SUD (41). Further, the authors found that ED visits due to BDZ were followed by hospitalization more often than opioid-related ones (41).

Several studies addressed the association between BDZ abuse and mental diseases, other SUD, and suicide (40, 42-44). Votaw et al. (43) highlighted that (i) BDZ are commonly consumed with other substances; (ii) misuse is common, because of difficulties in coping with depression and sleep disorders; (iii) misuse can cause morbidity and mortality. Besides the commonly reported predictors of BDZ abuse, Kan and coauthors (42) identified the main risk factors of BDZ dependence to be (1) being a self-help patient; (2) higher dose, longer duration of BZD use, (3) young age; (4) non-native cultural origin, (5) lower level of education, and (6) being in outpatient treatment for alcohol or drug dependence. Also, the pattern of prescription drug misuse varies across the life span, with a peak in adolescence and young adulthood (44). Additional information is reported in Table 3.

Clarification on the definitions of different types of inappropriate use of BDZ is provided in Supplementary Table 1.

IMPORTANCE OF GOOD PRESCRIBING PRINCIPLES AND CONCRETE OBSTACLES

BDZ's therapeutic character plays a role in the misperception of their hazard. In fact, the undervaluation of the risks is implied in their inappropriate use, both under and outside prescription (23). BDZ are symptomatic drugs, whose use needs to be temporary and strictly controlled by a

physician (23). The SUD risk assessment could be considered before newly prescribing BDZ, weighting risks and benefits, and identify the best BDZ for the individual patient. Several examples of risk assessment tools were provided by the Substance Use Guideline Committee of the New York State Department of Health AIDS Institute (NYSDOH AI) (45). To date, there is no international consensus on the maximum therapeutic dose for BDZ, and further pharmaco-epidemiological studies are needed to clarify the toxic thresholds of the different BDZ types (46). For all these reasons, BDZ use needs high awareness and careful management from the physician and the patient, who need to be informed on their mechanism of effect and their potential adverse events, including addiction (23). BDZ prescription deserve a specific and well-developed recording system as well (47,48). Mandatory prescription drug monitoring programs have been proposed to this aim, and their effects were evaluated in recent studies, showing inconsistent results (49-52). To favor the good prescribing, general guidelines on BDZ use should be made accessible to both the general practitioner and the population (53). This might also sensitize to inappropriate BDZ use and contribute to lowering stigma and self-stigma towards BDZ (54).

In autumn 2020, the Food and Drug Administration (FDA) published a communication on the update of warning to improve safe use of BDZ, where they reported that *"current prescribing information for BDZ does not provide adequate warnings"* towards the serious risks of abuse, addiction, physical dependence and withdrawal reactions which accompany BDZ use, and that "*stopping them abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening"* (23).

Availability of BDZ is also an important aspect when investigating the epidemiology of their inappropriate use. Some subgroups of people have simplified access to BDZ. Among these, there are health care workers (HCW), and in particular physicians, who in many countries can self-prescribe medications (55-58). This might be referred, at least in part, to the prevalence of burnout symptoms and sleep disorders among HCW (59,60). Given their facilitated access to the drug, and the risk-profile of this population, HCW are a category which is exposed to the risk of BDZ inappropriate use. This is supported by current literature: a study reported higher use of substances in association to night shifts and rotating shift work in nurses (61). Another study found that 9% of resident physician under night shift work reported to use BDZ to sleep (62). Also, 49% prevalence of BDZ use was recently reported among resident physicians in a Pakistan hospital, with alprazolam being the most used (63). The pattern of BDZ use among nurses has been described in Taiwan, with higher prevalence of use in association to depression, anxiety and sleep disorders (64). Burnout was analyzed

in relation to anxiolytics and antidepressants use in Spain, resulting in a significant association among nurses (65).

The social stigma linked to mental health, including anxiety, distress, and difficulty in coping, is especially emphasized in the working setting (66). Use of psychotropic medication may, in fact, raise concern during the work ability assessment (66). This can result in reluctance to seek for adequate treatment, delaying it and, in certain subjects, enhancing the likelihood of self-treatment (66). For example, the prevalence of self-treatment with psychotropic drugs among more than 2000 resident physicians in France was around 22%, according to a recent study (67). HCW affected by problems related to BDZ inappropriate use may experience difficulties at work due to cognitive impairment and be afraid of the potential legal implications (68). This finds support in public evidence, which shows that BDZ use is usually under-reported to both the general and the occupational physician, and reluctance to seek mental health treatment is common (66-68). Notably, stigma also represents a barrier to an accurate documentation of this phenomenon in the workers.

When looking at BDZ use in a population, national regulations need to be accounted for. For example, in Italy BDZ are not covered by the National Health System (contrary to the less commonly used opioids), but are available under medical prescription for affordable cost. The easy, non-strictly monitored access to BDZ results in a less controlled purchase, and a lack of ambulatory follow-up (41). Japan, which registers among the highest consumption of BDZ among the high-income countries, lacks a nationwide electronic health record system, preventing physicians from tracking prescription of medications which might have already been granted during previous visits (69), in a practice called “doctor shopping” aimed at obtaining multiple prescriptions (70). As a solution to this phenomenon, the Japanese Government has recently decided to abolish the current health insurance card in autumn 2024, to shift the use of My Number cards – Japan national identification system - with health insurance certificate functions (69, 71). This will have, among the benefits, a better monitoring of the purchase of medications.

BENZODIAZEPINE AND MORTALITY RISK

Risk factors of benzodiazepine-related deaths

The abuse of BDZ is a risk in subjects who are exposed to this drug without prescription or adequate follow-up, and may lead to life-threatening outcomes. Concern around BDZ-related overdose death has been raised by a recent report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA [72]). This shows that more than half of the drug-related death recorded in the UK in 2017 implicated BDZ, especially the newly developed etizolam (72). Particular concern was raised on the use of alprazolam, which demonstrated higher toxicity in overdose compared to other BDZ (73). Several studies reported a correlation between prevalence of BDZ use and death (Table 4, [74-80]). Notably, misclassification of unintentional and intentional poisoning may prevent from understanding the predictors of both and targeting intervention for their prevention (81).

The problem of BDZ-associated mortality is mainly due to concomitant use of other substances (75). Among the most commonly associated with BDZ inappropriate use are opioids and alcohol (75, 82). While the negative effect of contemporary assumption of BDZ and alcohol is well known, the magnitude of its risk is not clear in the general population. Interestingly, a recent study reported higher mortality rates related to BDZ use after cannabis legalization in the US, which is suggestive of a pattern of risk observed in multi-substance users (83).

Large population-based cohort studies have found a significant effect of BDZ on all-cause mortality (76). Co-prescription markedly increase the probability of life-threatening outcomes in BDZ users (75). Park et al. found that 27% of a cohort of US Veterans from the Veteran Health Administration (VHA) were prescribed with BDZ, and about half of the deaths occurred when veterans were co-prescribed with opioids (78). History of BDZ prescription was associated to mortality, with a dose-response effect (78). Anyway, the lack of adjustment by psychiatric conditions impaired the analysis, with possible discrepancies in mortality among BDZ users and non-users based on mental health conditions (78).

In a previous cohort study conducted on about 3,300,000 patients from the VHA, non-substance-related psychiatric disorders remained significantly associated to increased risk of death by accidental overdose after adjusting for SUD, suggesting an independent effect of mental disorder (79). On the contrary, a subsequent study highlighted how the known relation between SUD and suicide was attenuated when adjusting by psychiatric disorders (81). Therefore, the careful investigation of

prospectively collected data on different subgroups, with and without major psychiatric comorbidities, is required to provide important knowledge on BDZ adverse events and their predictors.

Intentional or unintentional overdose

When death from BDZ overdose occurs, it is often difficult to distinguish whether it had an unintentional or intentional basis, thus if it is case of suicide. Intentionality in drug overdose death takes different nuances as it can be seen in terms of (i) association or causal role of BDZ in the death; (ii) psychiatric comorbidities explaining suicidal ideation, or indifference toward deaths; (iii) other comorbidities acting as death facilitators; (iv) medico-legal issue of overdose death classification. Retrospective studies have consistently shown that hypnotic users are overrepresented among suicide victims (84). Mc Call et al. found an association between BDZ and suicide (84). Some European studies reported a proportion of deaths to be attributable to BDZ as single agent. Nevertheless, the intentionality of the recorded deaths and the actual absence of concomitant alcohol ingestion remain difficult to assess.

Symptoms typical of major depression, such as negative mood and hopelessness, may result in a tendency to undervalue risks, including those related to substance use (90). In this sense, the accidental or unintentional overdose may not be a suicide attempt, but rather the result of an indifference toward death, in contrast with a desire to die.

Coingestion of drugs or alcohol are more frequently associated to more severe outcomes including death, and more frequently reported in suicidal attempts (38, 85). Anyway, given the largely altered perception of the risk in long-term BDZ users, deaths from BDZ overdose should not be referred as suicidal without an accurate and multidimensional analysis of the specific case (86). Moreover, additional factors such as lifestyle habits (87-90) (smoking, alcohol, nutritional status, sleeping patterns) and concomitant diseases (91-95) (eg., chronic respiratory disease, obstructive sleep apnea, neurological conditions, arrythmia and myocardial infarction) can play a role in the severity of the outcome in the subject with BDZ-related disorders. In fact, as many subjects with SUD adopt unhealthy lifestyles, their physical condition at the moment of overdose are not physiological (93). The marked weakness of the subject who may suffer from BDZ overdose and/or withdrawal represent a factor of high vulnerability, where BDZ abuse and its consequences can become the determinant of passing the breaking point, possibly leading to death. Higher mortality in correlation to BDZ use has

been described in patients affected from chronic lung and kidney disease, schizophrenic patients, subjects with SUD and the elderly (7).

The classification of death from overdose as intentional or unintentional is an open medical-legal issue. The legal determination of intent on drug-related poisoning deaths in Australia (81) and in the US (96) has been shown to vary by local jurisdictions and by time, with increase in deaths classified as unintentional. Commonly, drug-related deaths are recorded as unintentional (eg., 55.6% in the Australian analysis [81]). The difficulty in establishing the intentionality of the cause of death from BDZ use influences the reliability of ICD codes records, and therefore the estimates of the number of accidental deaths from BDZ use.

ADDRESSING THE PROBLEM OF BENZODIAZEPINE INAPPROPRIATE USE

The identification of high-risk subgroups who could benefit from prevention and treatment appears of outmost importance for primary and secondary prevention of BDZ abuse. First, BDZ overdose and withdrawal syndrome should be suspected in ED visits. Screening for SUD through brief questionnaires could help in the differential diagnosis with other conditions. For example, the use of a brief tablet-based screening tool, consisting of a 7-point questionnaire including the use of BDZ, resulted to be effective in identifying patients with SUD in an ED of a trauma care center in California (97). The introduction of such tools in appropriate settings would contribute to the identification of subjects who suffer from SUD, and to identify episodes related to overdose or withdrawal.

Researchers have focused on the development of innovative, highly sensitive, and accurate methods to detect BZD and their metabolites (98). Their determination in biological fluids is essential in clinical assays, as well as in forensics and toxicological studies (93). Commonly used biological specimens for these analyses are blood, urine, and saliva. Currently, there are 2 types of BZD analysis: 1, the screening (qualitative or semiquantitative methods) and 2, the dosage (quantitative methods) (98). Designer BDZ are particularly difficult to detect in toxicological examinations (99,100). They include pharmaceutical drug candidates that have never been approved for medical use (59,101). These molecules are part of the novel psychoactive substances which share chemical structure characteristics of traditional BDZ, but have different functional groups, which makes them escape from the detection through routine laboratory analyses in either forensic laboratories or in workplace,

probation, or prison drug testing (58). The use of this class of drugs contributes to the number of life-threatening events, and the proportion of unrecognized cases, related to BDZ inappropriate use.

The development of specific discontinuation programs helps in controlling SUD (102). Many alternate drug therapies have been proposed to reduce the severity of withdrawal, including alpha-blockers (propranolol and clonidine), anticonvulsants (valproic acid, lamotrigine, carbamazepine, and phenobarbital), progesterone, baclofen, and trazodone (21). No statistically significant advantage to BZD therapy was observed (21). The current treatment of choice is to switch the current short-acting BZD for a long-acting alternative then gradually taper the dose to wean the individual off BZD completely (21). Baandrup et al. could not draw solid conclusions on discontinuation treatments due to the limited number of trials using a specific drug and the small number of participants in these studies, suggesting the necessity of further development in this field of research (103). In fact, long-term effectiveness of BDZ discontinuation remains difficult to describe (104). A new promising approach is blended-care, defined as combining face-to-face consultations with the general practitioner with web-based self-learning by the patient. This latter consists of a sleeping diary, a tapering schedule, and psychoeducation modules for the patient to favor the resolution of baseline symptoms and reinforce positive behaviors. Studies have shown that the combination of dose-tapering and psychotherapy interventions, self-help instructions and patient education produces better outcomes compared to stand-alone strategies (53, 104).

While treatment of BDZ dependence should be a goal, the potentially detrimental consequences should be also considered. Maust et al. recently published the results of their comparative effectiveness study conducted over more than 350,000 US long-term BDZ users, which led to unexpected results: the analysis showed a 1.6-fold higher risk of mortality in discontinuers than in non-discontinuers, as well as higher likelihood of non-fatal overdoses, suicidal ideation, and ED admission (105). This could be either due to the withdrawal-related adverse effects, or to the shift to other substances of abuse by the patients (105). While such results need to be replicated to better clarify this association, they reveal potential unintended harm of discontinuation in long-term BDZ users, underlining the importance of prevention of BDZ addiction (105).

Predictors of discontinuation might be identified. Younger patients tend to have a decreased success rate of discontinuing BZD use than older patients (105), while alcohol use did not result to impact discontinuation. Also, particular genetic high-risk profiles have been associated to life-threatening

outcomes of withdrawal syndrome (105). Besides this, the adherence to such interventions relies also on the receptiveness of the subjects, where an indifferent attitude towards death leads to underestimation of risks and unhealthy behaviors (106,107).

CONCLUSIONS

BDZ inappropriate medical and non-medical use can lead to several adverse outcomes, including life-threatening events. The control of BDZ use should be multidimensional, involving different professional figures, as well as laws on drugs costs and selling, public educational programs on their potential harms, training of the physicians on the good prescribing practice and the epidemiology of adverse outcomes related to BDZ abuse (108,109). The crucial point in relation to adverse outcomes related to BDZ is to prevent their inappropriate use. Prospective studies on the topic are fundamental to define the magnitude of BDZ inappropriate use and the related outcomes, and would help in the development of specific support programs for targeted vulnerable individuals.

Declarations

Conflict of Interest

The authors declare there is no conflict of interest.

Author Contributions

Conceptualization: GC. Investigation: GC, SM, AG. Methodology: PB, GC. Writing the main draft: GC. Writing review and editing: all authors. SM provided important insight and expertise to this work. All authors reviewed and approved the final version of the manuscript.

Table 1. Epidemiology of benzodiazepine and different uses

Study	Design	Country	Years	Type of use	Prevalence	Information
Bais et al., 2020 (10)	Systematic review and meta-analysis	Worldwide	Until July 2019	During pregnancy (12 months before, during, and 12 months after pregnancy)	1.9% (95%CI 1.6%-2.2%; I2 97.48%)	Most prescribed: lorazepam (1.5%, 95% CI 0.5%-2.5%; I2 99.87%)
Airagnes et al., 2019 (11)	Cohort study including 4686 men and 4849 women	France	2009-2015	Long term use (anxiety and depression)	Men: 2.8% (95% CI:2.3-3.4); women: 3.8% (95% CI: 3.3-4.5)	Women had an increased risk of BDZ long-term use (OR=1.34, 95% CI=1.02-1.76). Vulnerability factors: aging, low education, not being at-work, low occupational grade, low income, being alone and depressive state
Lukacisinovà et al., 2021 (12)	Cross-sectional	Europe+ Israel	2009-2014	4,156 nursing home ≥65 residents	From 14,5% in Germany to 44.1% in Israel	Most prescribed: zopiclone (17.8%), lorazepam (17.1%), oxazepam (16.3%)
Maust et al., 2018 (13)	Cross-sectional	US	2015-2016	86,186 adult civilians, non-istitutionalized	Average 5%	BDZ use prevalence: 12.6% (95% CI=12.2%−12.9%), including misuse 2.2% (CI=2.0%−2.3%) and use as prescribed 10.4% (95% CI=10.1%−10.7%). Use among adults ages 50–64 was highest. Most BDZ use among 18–25 aged was misuse (5.2%, 95% CI=4.8%−5.6%). Misuse was reported by just 0.6% (95% CI=0.4%–0.8%) of ≥65 aged. Most misused: alprazolam.

CI, confidence interval; BDZ, benzodiazepine

[1] referring to two or more psychoactive substances and use of other psychoactive substances, or neonatal withdrawal symptoms from maternal use of drugs of addiction, as well as the detection of hallucinogen, other potential addictive drugs, psychotropic drug, steroid, abnormal heavy metal content or lithium in the blood

Table 2. Overview on side adverse events related to use of benzodiazepine, and important implications in medical practice.

Side effects related to BDZ (15-18)	Decline in cognitive impairment in domains including: - Receptive Language - Expressive Language - Recent Memory - Visuoconstruction - Divided Attention - Processing Speed - Working Memory Falls, motor vehicle crashes, hip fracture In pregnant women: risk of premature birth, low birth weight, spontaneous abortion, low Apgar score, Neonatal Intensive Care Unit admission.	
Consequences of BDZ abuse	Loss of money to buy drugs, high healthcare costs, intrafamilial problems, job loss, legal issues, work impairment, decreased working productivity, demotion, dismissal, compromised ability in daily issues and choices	
Major events (19-24)	**Overdose**	**Withdrawal syndrome**
BDZ-related	*Isolated BDZ overdose:* CNS depression with normal vital signs, slurred speech, ataxia, altered mental status (with high dose), cardiac-related effects and	*Psychological symptoms:* sleep disturbance, nightmares, irritability, increased tension and anxiety, panic attacks, paranoid thoughts, social phobia, poor memory, poor concentration, catatonia (inability to speak, rigid body, repetitive and meaningless movements), mania (euphoria,

	fatalities (rare). Possible respiratory depression*. *Uncommon in isolated BDZ ingestion, but frequent in concomitant ethanol intake. Its occurrence depends on multiple factors, including dosage, tolerance, weight, age, coingestion of other drugs, genetics. *Severe toxicity*: stuporous or comatose state requiring immediate airway management and mechanical ventilation. *Overdose from coingestion of BDZ and other drugs*: life-threatening respiratory depression which requires immediate intervention. *Iatrogenic BDZ toxicity*: condition which may occur when BDZ are combined with other drugs (eg. opiates) during procedural sedation.	delusions, overactivity), psychosis (false beliefs), delirium tremens (shaking, shivering, irregular heartrate, sweating). *Physical symptoms*: headache, seizures, hand tremor, sweating, dry retching and nausea, abdominal distension, changes in defecation, appetite change, weight loss, palpitations, headache, muscular pain and stiffness, weakness and fatigue, tingling and numbness, muscle twitches, gastrointestinal symptoms. For high doses: seizures and psychotic reactions. Most common pattern: short-lived "rebound" anxiety and insomnia, within 1-4 days of discontinuation, depending on the half-life of the particular drug. Second pattern: full-blown withdrawal syndrome, lasting 10-14 days. Third pattern: return of anxiety symptoms persisting until treatment initiation. Seizures, hallucinations and suicide typically result from over-rapid tapering or abrupt cessation. These symptoms may last for one to a few weeks after cessation, with duration and severity largely depending upon duration of BZD use, half-life of the specific BZD, and daily dose. Predictors for more severe withdrawal syndrome: high doses, long duration, potency of BDZ, short-acting BDZ, baseline anxiety
Differential diagnosis (19)	Alcohol toxicity, hypoglycemia, hyponatriemia or hypernatriemia, stroke, opiate toxicity, other substances toxicity.	
Red flags (20)	Increasing use of medical services. Frequent appointments to the emergency department. Repeated visits to primary care without resolution, referrals to multiple specialists. Explanations that are somatic in nature like conversion disorder, health anxiety or hypochondria may be suggested or implied.	

Notes: BDZ, benzodiazepines; CNS, central nervous system;

Table 3. Risk factors of benzodiazepine abuse.

Risk factors
Genetic, environmental, white/non-latino ethnicity, deprived neighborhood, low educational level, substance use disorder, multiple use of drugs, mental disease, difficulties in coping with stress, anxiety, sleep disorders, young age, being a self-help patient, higher dose, longer duration of use, non-native cultural origine

Table 4. Selected studies investigating the risk of death from overdose implying benzodiazepine use.

Study	Country	Population	Years considered	Prevalence of BDZ use	N/% OR/ death	Notes
Oh TK et al., 2021 (74)	South Korea	N=822,414; BDZ group N=30,837; control group N= 791,377;	BDZ use 2010-2015; Mortality 2011-2015	3.80% in the total population	BDZ group: 10.0% Control group: 9.4%; Five-year all-cause-mortality: HR=1.15 (95% CI=1.09-1.22)	BDZ users= all subjects prescribed continuously or 30 days at least Adjusted for: age, sex, income, place of residence, Charlson comorbidity index, number of outpatient clinic visits in 2010 (day) Results based on analyses performed on 61672 matched individuals (30836 in each group)
Figgatt MC et al., 2021 (75)	US (North Carolina)	North Carolina population	2009-2018 death certificates	BDZ involved in 20.2% of deaths from overdose	BDZ+opioids N=1084; BDZ+stimulants+opioids N=366; BDZ+antiepileptics+opioids N=259	Most frequently identified substances: opioids (84.3%), stimulants (30.3%), BDZ (20.2%), alcohol (12.2%), antiepileptics (8.4%), and other substances (9.5%) Polysubstance overdose accounted for 52.5% of all fatal overdoses. Increased trend in unintentional polysubstance overdose: from 31.6% in 2009 to 62.3% in 2018. Most common combination of drugs: opioids + stimulants 12.1%; opioids + BDZ 9.0%; opioids + alcohol 5.1%; opioids + stimulants + BDZ 3.1%; opioids. +BDZ + antiepileptics 2.2% of overdose deaths.
Kripke et al., 2012 (76)	US	10,531 patients prescribed with hyponotics vs 23,676 matched controls	Average of 2.5 years between January 2002 and January 2007	1:2 matched cases and controls	6.1% of hypnotic users vs 1.2% of controls died during the observation period	The association remained remained consistent using multiple strategies and after accounting for important confounders, including major

					0.4-18 pills/year, HR=3.60 (95% CI=2.92-4.44) 18-132 pills/year, HR=4.43 (95% CI=3.67-5.36) >132 pills/year, HR=5.32 (95% CI=4.50-6.30) For zolpidem only: 3.93 (95% CI=2.98-5.17), 4.54 (95% CI=3.46-5.95), 5.69 (95% CI=4.58-7.07)	comorbidities, but models were not adjusted by psychiatric disorders like depression and anxiety. Zolpidem was the most prescribed hypnotic. A linear increased risk of cancer was observed for 18-132 pills/year and >32 pills/year. This risk was higher for temazepam users than zolpidem users.
Weich S et al., 2014 (77)	UK	34,727 patients prescribed with anxiolytics and/or hypnotics vs 69,418 controls	Deaths 1998-2001	BDZ only: N=16, 242 (46.8%) BDZ+Z drugs: N= 6,305 (18.2%) BDZ+other: N=2.169 (6.3%) BDZ+Z+other: N=1.720 (5.0%)	HR of death for drugs vs no drugs before and after adjusting for potential confounders: DDDs (all study drugs): 0 1.00 1-30 1.89 (95% CI=1.80-1.98) 2.07 (95% CI=1.97-2.17)* 31-60 2.38 (95% CI=2.25-2.51) 2.58 (95% CI=2.44-2.72)* 61-90 2.39 (95% CI=2.23-2.56) 2.46 (95% CI=2.29-2.63)* ≥91 1.77 (95% CI=1.72-1.84) 1.91 (95% CI=1.84-1.98)* Any DDDs 1.93 (95% CI=1.87-1.98) 2.08 (95% CI=2.02-2.15)*	*Adjusted for age, sex, physical health problems, psychiatric disorders, and prescriptions for non-study drugs.

Park TW et al., 2015 (78)	US	422,786 US veterans receiving opioids analgesics from the VHA	Deaths recorded in 2004-2009	27% (N=122,069) of subjects received also BDZ	Total deaths from drug overdose N=2400; Deaths in BDZ users: N=1185, 49%. N=1185 deaths occurring in BDZ+opioids users; Death risk and history of BDZ prescription: HR=2.33 (95% CI=2.05-2.64) for former prescription vs no prescription; HR=3.86 (95% CI=3.49-4.26) for current prescription vs no prescription Dose-response relationship was observed, with HR=3.06 (95% CI=2.38-3.92) for >40 g/day BDZ compared to 0-10 mg/day.	BDZ dosing schedule was not associated with risk of death from drug overdose. Adjusted for: sex, age, race, ethnicity, area level poverty, time varying daily opioid dose, recent admission to hospital related to SUD, Charlson comorbidity index, diagnosis of SUD, post-traumatic stress disorder, other anxiety disorder, depression, bipolar/psychotic disorder, and cancer, and use of other drugs. SUD was more frequent in BDZ users than non-users (13% vs 10%). Recent hospital admission for mental health issues/SUD was more frequent in BDZ users than non-users (4% vs 1%) Most commonly prescribed BDZ: alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, and temazepam.
Bohnert ASB et al., 2012 (79)	US	All US veterans patients treated in VHA during fiscal year 1999 and alive at the start of fiscal year 2000 (n=3,292,891)	Deaths 2000-2006	Overall prevalence of BDZ use not available. Drug use disorders: 5.7% in overall population, 43.5% in subjects died from accidental overdose.	Medication-related accidental overdose death associated with "other drug" use disorder: HR=4.56 (95% CI=4.14-5.03)	Death by accidental overdose was determined using National Death Index records and defined as ICD-10 codes X40-X45 (N=4,485). Diagnoses were determined by patient medical records. Adjusted for: age, sex, Charlson comorbidity score, and Veterans Affairs priority status. Medication-related and alcohol/illegal drug-related overdoses are not mutually exclusive.
Bohnert KM et al., 2017 (80)	US	All VHA users in fiscal year 2005 who were alive at the beginning of fiscal year 2006 (n = 4,863,086).	2006-2011 for mortality; 2004-2005 for SUD	SUD diagnosis males = 8.4%; females = 3.4%	Suicide n=9,087; The suicide rate among individuals with SUD diagnosis was 75.6 per 100 000 person-years, in particular 76.1 per 100,000 person-years for males	The highest suicide rate was observed in sedative/hypnotic/anxiolytic users. Adjusted for age, Charlson Comorbidity Index, psychiatric diagnosis

					and 63.4 per 100,000 person-years for females. Sedative, hypnotic, anxiolytic use disorder: suicide rate per 100,000 persons-years =171.4 (174.1 in men and 138.7 in women) Suicide HR=1.97 (95% CI=1.51-2.57) in men; HR=2.41 (95% CI=0.79-7.44) in women	

BDZ, benzodiazepine; N, number; OR, Odds Ratio; HR, Hazard Ratio; DDD, definite daily dose; CI, Confidence Interval; VHA,Veteran Health Administration; SUD, substance use disorder

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